MAIL STOP APPEAL BRIEF-PATENTS
Attorney Docket No. B100001XY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

BURNETT *et al.* | Confirmation No. 4660

Serial No.: 10/722,134 | Group Art Unit: 1617

Filed: November 26, 2003 | Examiner: CARTER, Kendra D.

For: **ANHYDROUS TOPICAL SKIN PREPARATIONS**

AMENDED APPEAL BRIEF UNDER 37 C.F.R. § 41.37

This brief is being filed in the above-identified patent application further to a Notice of Appeal filed on August 1, 2007. This amended appeal brief is submitted in response to the notification of non-compliant appeal brief mailed December 18, 2008. The period for filing this brief has been extended through February 18, 2009 by the filing of a petition for a one-month extension of time and fee. Accordingly, this appeal brief is timely filed.

1. **Table of Contents**

2. The Real Party in Interest

The real party in interest in this appeal is Barrier Therapeutics, Inc. of Princeton, New Jersey, which has a license to the present invention from Johnson & Johnson Consumer Products Inc. of Skillman, New Jersey.

3. **Related Appeals and Interferences**

Appellants are not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 1 to 38, 43, 73

Claims withdrawn from consideration but not cancelled: None

Claims pending: 39 to 42, 44 to 72 and 74 to 84

Claims objected to: None

Claims allowed: None

Claims rejected: 39 to 42, 44 to 72 and 74 to 84

The claims on appeal are 39 to 42, 44 to 72 and 74 to 83.

5. Status of Amendments

Appellants filed an Amendment and Response on November 20, 2006 in which claims 39, 72, 74, 77 and 81 were amended and claim 84 was added. The Examiner subsequently issued an Office Action dated February 1, 2007 in which the amendments were entered but the rejection of all claims was maintained. As such, Appellants submit that claims 39 to 42, 44 to 72 and 74 to 84 are the currently pending claims of record. The claims listed in the claims appendix herein incorporate the claim amendments of the aforementioned Amendment and Response.

6. Summary of Claimed Subject Matter

The present invention relates to novel, unobvious anhydrous topical formulations containing ketoconazole.

In particular, pending independent claim 39 claims an anhydrous composition formulated for topical delivery comprising: (a) about 1 to about 50 percent by weight of ethanol, (b) propylene glycol, (c) polyethylene glycol, (d) glycerin, and (e) ketoconazole. Basis for this claim is found, for example, on page 3, line 16, to page 4, line 3; page 4, lines 14-15; page 5, lines 14-16; page 6, lines 8-10; and page 8, lines 3-16.

Independent claim 72 claims an anhydrous composition formulated for topical delivery comprising: (a) propylene glycol, (b) polyethylene glycol, (c) glycerin, (d) about 1 to about 50 percent by weight of ethanol, (e) ketoconazole, (f) PPG-15 stearyl ether, (g) hydroxypropyl cellulose, (h) ascorbic acid, (i) butylated hydroxytoluene, and (j) citric acid. Basis for this claim is found, for example, on page 8, lines 3-16.

Further, independent claim 84 claims an anhydrous composition formulated for topical delivery comprising: (a) about 1 to about 50 percent by weight of ethanol, (b) propylene glycol, (c) polyethylene glycol, (d) glycerin, and (e) ketoconazole. Basis for this claim is found, for example, on page 8, lines 3-16.

7. **Grounds of Rejection to be Reviewed on Appeal**

A. Rejection of claims 39-42, 44-62, 64, 66-71, 74, 75, 77-80 and 83 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Patent 5,993,787 to Sun *et al.* ("Sun"). The Examiner asserts that Sun teaches anhydrous topical preparations that comprise propylene carbonate, one or more short chain alcohols and/or glycols, glycerol and an active ingredient. The Examiner cites a section of the Sun specification wherein ketoconazole is disclosed as a suitable active ingredient and other sections where additional components such as pigments, ascorbic acid, BHT, chelating agents and hydroxypropyl cellulose are allegedly taught to be useful as well. The Examiner acknowledges that Sun does not explicitly disclose the particular combination of components claimed by Appellants but asserts that absent a showing of unexpected results, it would have been obvious to a person of ordinary skill in the art to prepare the composition claimed by Appellants.

B. Rejection of claims 63, 65 and 72 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Sun in view of U.S. Patent 5,208,257 to Kabara ("Kabara"). In addition to Sun, the Examiner relies on Kabara for its alleged teaching of chelating agents such as citric acid.

C. Rejection of claims 76, 81 and 82 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) over Sun in view of U.S. Patent 5,231,087 to Thornfeldt ("Thornfeldt"). In addition to Sun, the Examiner relies on Thornfeldt for its alleged teaching of the treatment of seborrheic dermatitis.

D. Rejection of claims 39-42, 44-51, 55-61, 63, 65-71 and 84 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over U.S. Patent 5,476,852 to Cauwenbergh *et al.* ("Cauwenbergh") in view of U.S. Patent 5,110,809 to Wang *et al.* ("Wang"). The Examiner asserts that Cauwenbergh teaches a topically applicable composition containing ketoconazole, and that does not contain a retinoid. The Examiner acknowledges that Cauwenbergh does not specifically teach providing an anhydrous gel carrier with propylene glycol and ethanol but asserts that Wang teaches a stable anhydrous gel formulation for topical antifungal use.

E. Rejection of claims 62 and 64 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Cauwenbergh in view of Wang and further in view of U.S. Patent 4,214,000 to Papa *et al.* ("Papa"). The Examiner acknowledges that Cauwenbergh and Wang do not specifically teach an anhydrous gel composition with ascorbic acid but relies on Papa for its alleged teaching of ascorbic acid.

F. Rejection of claims 52-54 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Cauwenbergh in view of Wang and further in view of U.S. Patent 5,292,530 to McCrea *et al.* ("McCrea"). The Examiner acknowledges that Cauwenbergh and Wang do not specifically teach an anhydrous gel composition with PPG-15 stearyl ether but relies on McCrea for its alleged teaching of PPG-15 stearyl ether.

G. Rejection of claim 72 under 35 U.S.C. § 103(a)

Whether the identified claim is unpatentable under 35 U.S.C. § 103(a) as obvious over Cauwenbergh in view of Wang and further in view of Papa and McCrea. The Examiner acknowledges that Cauwenbergh and Wang do not specifically teach an

anhydrous gel composition with ascorbic acid and PPG-15 stearyl ether but relies on Papa for its alleged teaching of ascorbic acid and on McCrea for its alleged teaching of PPG-15 stearyl ether.

H. Rejection of claims 74-83 under 35 U.S.C. § 103(a)

Whether the identified claims are unpatentable under 35 U.S.C. § 103(a) as obvious over Cauwenbergh in view of Wang and further in view of Thornfeldt. The Examiner acknowledges that Cauwenbergh and Wang do not specifically teach treating fungal disorders associated with *T. rubrum* or *P. ovale*, specifically seborrheic dermatitis, but relies on Thornfeldt for its alleged teaching of the significant role that *P. ovale* plays in seborrheic dermatitis in humans.

An outstanding written description rejection of claim 84 is not currently being appealed.

An obviousness-type double patenting rejection of claims 39-42, 44-72 and 84 over claims 1-3, 8-16, 22, 25 and 26 of U.S. Patent 6,238,683 is not currently being appealed.

An obviousness-type double patenting rejection of claims 74-83 over claims 1-3, 8-16, 22 and 24-26 of U.S. Patent 6,238,683 in view of Thornfeldt is not currently being appealed.

A provisional obvious-type double patenting rejection of claims 39-42, 44-72 and 74-84 over claims 48-53, 56-62 and 86-118 of copending Application No. 09/562,376 is not currently being appealed.

8. Argument

A. Rejection of claims 39-42, 44-62, 64, 66-71, 74, 75, 77-80 and 83 under 35 U.S.C. § 103(a) over Sun

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) over Sun is improper and should be reversed.

Appellants respectfully submit that Sun does not render Appellants' claimed invention obvious for at least the following reasons. Sun teaches compositions containing, *inter alia*, one or more short carbon chain alcohols and/or glycols including ethanol, isopropyl alcohol, propylene glycol, butylene glycol, hexylene glycol, polyethylene glycol, methoxpolyethylene glycol and their derivatives (col. 5, lines 25-29 of Sun, emphasis added). Based on this description in Sun, literally hundreds of compositions would be possible. Exemplary products 1, 2 and 3 are described as "formulated according to the present invention", but they each contain a higher amount of ethanol (55.87 wt %) than is allowed by Appellants' claims (see col. 10, line 32 to col. 11, line 3 of Sun). Therefore, there is no guidance for a person of ordinary skill in the art to select Appellant's particular claimed composition from the lists of components described in Sun.

Further, Appellant's claimed compositions show unexpected results. The Cauwenbergh declaration, which was submitted to the U.S. Patent Office in a response filed on November 20, 2006 and is now of record, testifies as to the experimentally determined anti-inflammatory superiority of an anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component compared to an otherwise identical anhydrous alcohol-based gel formulation of ketoconazole containing a steroidal component (see the graphs depicting comparisons of global scores and combination scores). Such results are completely unexpected and were not previously contemplated in Sun. In fact, Sun actually teaches away from compositions, like those claimed by Appellants (*i.e.*, compositions that do not include steroidal agents) by listing suitable steroidal anti-inflammatory agents for inclusion in the described compositions (see, *e.g.*, col. 6, line 58 to col. 7, line 16).

The Cauwenbergh declaration also documents the significantly lower cumulative irritation experienced by a patient who is being treated with Appellants' claimed anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component compared to a patient being treated with an aqueous formulation of ketoconazole (Nizoral®) also lacking a steroidal component. Such results contradict the predictions based on the conventional wisdom of a skilled artisan that an anhydrous alcohol-based formulation of a medicament should be significantly more irritating to skin than a water-based formulation of the same medicament.

The Cauwenbergh declaration also documents the superior overall efficacy of the anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component in treating patients afflicted with seborrheic dermatitis compared to the aqueous formulation of ketoconazole (Nizoral®) also lacking a steroidal component. Sun does not teach or suggest the above-discussed unexpected results associated with Appellants' claimed anhydrous alcohol-based gel composition. For at least the above-discussed reasons, Sun cannot therefore render obvious Appellants' claimed anhydrous compositions and Appellants respectfully request that this rejection be withdrawn.

B. Rejection of claims 63, 65 and 72 under 35 U.S.C. § 103(a) over Sun in view of Kabara

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

In light of the arguments presented in Section A above, Appellants submit that Sun does not render Appellants' claimed invention obvious. Kabara cannot remedy these deficiencies present in Sun. Accordingly, Appellants respectfully request that this rejection be withdrawn.

C. Rejection of claims 76, 81 and 82 under 35 U.S.C. § 103(a) over Sun in view of Thornfeldt

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

In light of the arguments presented in Section A above, Appellants submit that Sun does not render Appellants' claimed invention obvious. Thornfeldt cannot remedy these deficiencies present in Sun. Accordingly, Appellants respectfully request that this rejection be withdrawn.

D. Rejection of claims 39-42, 44-51, 55-61, 63, 65-71 and 84 under 35 U.S.C. § 103(a) over Cauwenbergh in view of Wang

Appellants respectfully disagree with the Examiner's rejection of the identified claims over the recited combination of references for at least the following reasons.

The Examiner asserts that the combination of Cauwenbergh with Wang would result in an anhydrous alcohol-based gel composition containing ketoconazole but no steroid. This reading of Cauwenbergh and Wang is contradictory to the individual teachings of the two references. Cauwenbergh teaches the use of aqueous formulations of ketoconazole for the treatment of acne. Aqueous formulations were chosen because it was known at the time that anhydrous alcohol-based formulations exacerbated skin inflammation, especially in disease states such as acne. Wang teaches both aqueous and anhydrous gel formulations of a combination of an imidazole agent and a steroid agent for the treatment of various fungal diseases. The steroidal component is necessary in the Wang formulations to alleviate the inflammation associated with the disease states being treated. Thus, a person of ordinary skill in the art would find no guidance to combine the anhydrous gel formulation teaching of Wang with the aqueous ketoconazole-only formulations taught by Cauwenbergh to generate an anhydrous alcohol-based gel formulation of ketoconazole that lacks a steroid agent because such a combination omits the inflammatory reducing steroid taught by Wang and the inflammatory reducing water component taught by Cauwenbergh. Given the knowledge at the time, there certainly would have been no reasonable expectation of success that such a formulation would provide an acceptable inflammation profile.

The previously recited Cauwenbergh declaration of record testifies as to the experimentally determined anti-inflammatory superiority of an anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component compared to an

otherwise identical anhydrous alcohol-based gel formulation of ketoconazole containing a steroidal component (see the graphs depicting comparisons of global scores and combination scores). Such results are completely unexpected and were not previously contemplated in the prior art. The Cauwenbergh declaration also documents the significantly lower cumulative irritation experienced by a patient who is being treated with Appellants' claimed anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component compared to a patient being treated with an aqueous formulation of ketoconazole (Nizoral®) also lacking a steroidal component. Such results contradict the predictions based on the conventional wisdom of a skilled artisan that an anhydrous alcohol-based formulation of a medicament should be significantly more irritating to skin than a water-based formulation of the same medicament. The Cauwenbergh declaration also documents the superior overall efficacy of the anhydrous alcohol-based gel formulation of ketoconazole lacking a steroidal component in treating patients afflicted with seborrheic dermatitis compared to the aqueous formulation of ketoconazole (Nizoral®) also lacking a steroidal component.

Neither Cauwenbergh nor Wang teach or suggest the above-discussed unexpected results associated with Appellants' claimed anhydrous alcohol-based gel composition that are described in the Cauwenbergh declaration. Accordingly, Appellants respectfully request that this rejection be withdrawn.

E. Rejection of claims 62 and 64 under 35 U.S.C. § 103(a) over Cauwenbergh in view of Wang and Papa

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

In light of the arguments presented in Section D above, Appellants submit that the combination of Cauwenbergh and Wang does not render Appellants' claimed invention obvious. Papa cannot remedy these deficiencies present in the combination of Cauwenbergh and Wang. Accordingly, Appellants respectfully request that this rejection be withdrawn.

F. Rejection of claims 52-54 under 35 U.S.C. § 103(a) over Cauwenbergh in view of Wang and McCrea

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

In light of the arguments presented in Section D above, Appellants submit that the combination of Cauwenbergh and Wang does not render Appellants' claimed invention obvious. McCrea cannot remedy these deficiencies present in the combination of Cauwenbergh and Wang. Accordingly, Appellants respectfully request that this rejection be withdrawn.

G. Rejection of claim 72 under 35 U.S.C. § 103(a) over Cauwenbergh in view of Wang and Papa and McCrea

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

In light of the arguments presented in Section D above, Appellants submit that the combination of Cauwenbergh and Wang does not render Appellants' claimed invention obvious. Papa and McCrea, either alone or in combination, cannot remedy these deficiencies present in the combination of Cauwenbergh and Wang. Accordingly, Appellants respectfully request that this rejection be withdrawn.

H. Rejection of claims 74-83 under 35 U.S.C. § 103(a) over Cauwenbergh in view of Wang and Thornfeldt

Appellants respectfully submit that the rejection of the identified claims under 35 U.S.C. § 103(a) is improper and should be reversed.

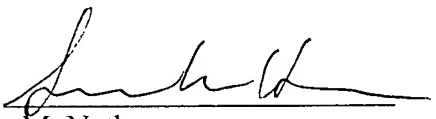
In light of the arguments presented in Section D above, Appellants submit that the combination of Cauwenbergh and Wang does not render Appellants' claimed invention obvious. Thornfeldt cannot remedy these deficiencies present in the combination of Cauwenbergh and Wang. Accordingly, Appellants respectfully request that this rejection be withdrawn.

In view of the foregoing, Appellants respectfully request the reversal of the Examiner's rejections and the allowance of the pending claims. If there are any other fees due in connection with the filing of this Appellants' Brief, please charge the fees to our Deposit Account No. 50-0310.

If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

By: 

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9. Claims Appendix

Claims 1-38 (cancelled).

Claim 39. An anhydrous composition formulated for topical delivery comprising:

(a) about 1 to about 50 percent by weight of ethanol,

(b) propylene glycol,

(c) polyethylene glycol,

(d) glycerin, and

(e) ketoconazole,

wherein the composition is formulated as an anhydrous gel and does not contain a retinoid or a steroid.

Claim 40. The composition of claim 39 wherein the ketoconazole is solubilized.

Claim 41. The composition of claim 39 wherein the amount of the ketoconazole is about 0.5 to about 3 percent by weight.

Claim 42. The composition of claim 39 wherein the amount of the ketoconazole is about 2.0 percent by weight.

Claim 43 (cancelled).

Claim 44. The composition of claim 39 wherein the amount of the polyethylene glycol is about 10 to about 80 percent by weight.

Claim 45. The composition of claim 44 wherein the amount of the polyethylene glycol is about 20 percent by weight.

Claim 46. The composition of claim 39 wherein the amount of the propylene glycol is about 1.0 to about 50 percent by weight.

Claim 47. The composition of claim 46 wherein the amount of the propylene glycol is about 20 percent by weight.

Claim 48. The composition of claim 39 wherein the amount of the glycerin is about 10 to about 80 percent by weight.

Claim 49. The composition of claim 48 wherein the amount of the glycerin is about 20 percent by weight.

Claim 50. The composition of claim 39 wherein the composition further comprises an emollient.

Claim 51. The composition of claim 50 wherein the amount of the emollient is between 0 and about 10 percent by weight.

Claim 52. The composition of claim 50 or claim 51, wherein the emollient is PPG-15 stearyl ether.

Claim 53. The composition of claim 52 wherein the amount of the PPG-15 stearyl ether is between 0 and about 2 percent by weight.

Claim 54. The composition of claim 53 wherein the amount of the PPG-15 stearyl ether is about 2 percent by weight.

Claim 55. The composition of claim 39 wherein the composition further comprises a viscosifier.

Claim 56. The composition of claim 55 wherein the amount of the viscosifier is between 0 and about 5 percent by weight.

Claim 57. The composition of claim 55 or claim 56 wherein the viscosifier is hydroxypropyl cellulose.

Claim 58. The composition of claim 57 wherein the amount of hydroxypropyl cellulose is about 1.5 to about 2.0 percent by weight.

Claim 59. The composition of claim 39 wherein the composition further comprises a pH adjuster.

Claim 60. The composition of claim 59 wherein the amount of the pH adjuster is between 0 and about 2 percent by weight.

Claim 61. The composition of claim 59 or claim 60 wherein the pH adjuster is selected from the group consisting of ascorbic acid, citric acid and combinations thereof.

Claim 62. The composition of claim 61 wherein the amount of the ascorbic acid is between 0 and about 0.3 percent by weight.

Claim 63. The composition of claim 61 wherein the amount of the citric acid is between 0 and about 0.5 percent by weight.

Claim 64. The composition of claim 62 wherein the amount of the ascorbic acid is about 0.3 percent by weight.

Claim 65. The composition of claim 63 wherein the amount of the citric acid is about 0.1 percent by weight.

Claim 66. The composition of claim 39 wherein the composition further comprises an antioxidant.

Claim 67. The composition of claim 66 wherein the amount of the antioxidant is between 0 and about 2 percent by weight.

Claim 68. The composition of claim 66 or claim 67 wherein the antioxidant is selected from the group consisting of ascorbic acid, butylated hydroxytoluene and combinations thereof.

Claim 69. The composition of claim 68 wherein the amount of the butylated hydroxytoluene is between 0 and about 0.1 percent by weight.

Claim 70. The composition of claim 69 wherein the amount of the butylated hydroxytoluene is about 0.1 percent by weight.

Claim 71 (previously presented): The composition of claim 39 wherein the composition further comprises one or more colorants.

Claim 72. An anhydrous composition formulated for topical delivery comprising:

(a) propylene glycol,

(b) polyethylene glycol,

(c) glycerin,

(d) about 1 to about 50 percent by weight of ethanol,

(e) ketoconazole,

(f) PPG-15 stearyl ether,

(g) hydroxypropyl cellulose,

(h) ascorbic acid,

(i) butylated hydroxytoluene, and

(j) citric acid,

wherein the composition is formulated as an anhydrous gel and does not contain a retinoid or a steroid.

Claim 73 (cancelled).

Claim 74. A method of delivering a composition of claim 39 or claim 72 for the treatment of skin fungal disorders to a recipient in need of such treatment comprising topically administering the composition to the recipient.

Claim 75. The method of claim 74 wherein the recipient is a human.

Claim 76. The method of claim 75 wherein the human is suffering from seborrheic dermatitis.

Claim 77. A method of treating skin fungal disorders comprising topically administering the composition of claim 39 or claim 72 to a recipient in need of such treatment.

Claim 78. The method of claim 77 wherein the recipient is a human.

Claim 79. The method of claim 78 wherein the skin fungal disorders are associated with *T. rubrum* or *P. ovale*.

Claim 80. The method of claim 79, wherein the skin fungal disorders are selected from the group consisting of tinea corporis, tinea cruria, tinea pedis and seborrheic dermatitis.

Claim 81. A method of treating seborrheic dermatitis comprising topically administering the composition of claim 39 or claim 72 to a recipient in need of such treatment.

Claim 82. The method of claim 81 wherein the recipient is a human.

Claim 83. The method of claim 74 wherein the skin fungal disorders are associated with *T. rubrum* or *P. ovale*.

Claim 84. An anhydrous composition formulated for topical delivery comprising:

(a) about 1 to about 50 percent by weight of ethanol,

(b) propylene glycol,

(c) polyethylene glycol,

(d) glycerin, and

(e) ketoconazole,

wherein the composition is formulated as an anhydrous gel and does not contain a retinoid, a steroid or propylene carbonate.

10. Evidence Appendix

A declaration under 37 C.F.R. 1.132 by Geert Cauwenbergh was submitted with an amendment that was filed on November 20, 2006 concurrently with a Request for Continued Examination. A subsequently issued Office Action on February 1, 2007 noted on page 29 the entry of the declaration into the record.

11. Related Proceedings Appendix

No information is appended under this section.

PATENT
Attorney Docket **054824-5001-01**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **K.M. Burnett *et al.***	)	
Application No. **09/562,376**	)	Art Unit: **1617**
Filed: **May 1, 2000**	)	Examiner: **Abigail M. Cotton**
For: **Anhydrous Topical Skin Preparations**	)	

DECLARATION OF GEERT CAUWENBERGH UNDER 37 C.F.R. 1.132

I, Geert Cauwenbergh, declare that:

1. I am currently the Chief Executive Officer and founder of Barrier Therapeutics ("Barrier"). I am also Member and Secretary of the Board of Trustees of the Biotechnology Council of New Jersey and a Board Member of the New Jersey Center of Life Sciences and also serve as an Official Trade Advisor to the Belgian Government for Health Care in the USA. Prior to founding Barrier, I was Vice President of Technology of the Johnson & Johnson ("J&J") Consumer and Personal Care Products Companies, where I created technology platforms based on intellectual property and know-how owned by J&J and developed a business proposition around these platforms as the basis for new companies or new businesses within J&J. I also served as Vice President of Research & Development of the J&J Consumer Companies Worldwide, managing a global organization of over 100 people, with an annual budget of $35 million, and was also a member of the J&J Business Development Council. I was also the Director of the Corporate Skin Care Council of J&J, coordinating the skin care activities in the different operating groups of the Corporation. Earlier in my career, I held positions in sales, and national and international marketing and was responsible for the successful global introduction of Nizoral® (ketoconazole cream). I joined the R&D organization of the Janssen Research Foundation in 1982, where I held positions of increasing global responsibility and oversaw the development of drugs such as Sporanox®, Nizoral® Shampoo, Terazol® and topical Sufrexa®. My R&D activities have also related to the fields of psoriasis, acne, wound healing, atopic dermatitis, protozoal infections and HIV. I have authored over 100 publications and have co-authored several books. I received my Ph.D. in Medical Sciences from the Catholic University of Leuven, Faculty of Medicine. A copy of my curriculum vitae is attached as Exhibit A.

2. I have reviewed the Office Action dated July 25, 2006 and in particular the Examiner's rejection of claims 49, 51, 52, 57 to 62, 89, 90, 94, 98 to 101, 105 and 134 to 136, drawn to anhydrous gel

compositions, as obvious over the combined disclosures of U.S. Patents 5,476,852; 5,110,809; 4,214,000; and 5,292,530.

3. That as part of my duties as Chief Executive Officer of Barrier, I had those under my direction and control conduct the three below-described studies demonstrating the unexpected overall superiority of the claimed compositions of an anhydrous gel formulation of ketoconazole compared to an aqueous formulation of ketoconazole and an anhydrous gel formulation of ketoconazole and the steroid desonide. For purposes of this declaration, these three studies will be labeled as "Antiinflammatory Study", "Cumulative Irritation Study" and "Antifungal Activity Study". For each study, the tested compositions were an anhydrous topical gel product containing a combination of 2% ketoconazole and 0.05% desonide ("Combination Product"), an anhydrous topical gel product containing 2% ketoconazole ("the Ketoconazole Product"), an anhydrous topical gel product containing 0.05% desonide ("the Desonide Product") and a placebo containing just the anhydrous gel vehicle ("the Placebo Gel Vehicle"). The Cumulative Irritation Study and the Antifungal Activity Study additionally included an aqueous cream-based formulation of ketoconazole, sold commercially as Nizoral® ("the Nizoral® Product"). The exact formulations of these products are shown below:

"the Combination Product"

Component	Weight %
ketoconazole	2.0000
desonide	0.0500
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 33.9477
	100.0000

"the Ketoconazole Product"

Component	Weight %
ketoconazole	2.0000
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 33.9977
	100.0000

"the Desonide Product"

Component	Weight %
desonide	0.0500
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 35.9477
	100.0000

"the Placebo Gel Vehicle"

Component	Weight %
polyethylene glycol 400	20.0000
propylene glycol	20.0000
glycerin	20.0000
PPG-15 stearyl ether	2.0000
hydroxylpropyl cellulose	1.5000
ascorbic acid	0.3000
butylated hydroxytoluene	0.1000
citric acid, monohydrate	0.1000
FD&C Yellow No. 6	0.0013
D&C Yellow No. 10	0.0010
Alcohol 200 proof	(QS) 35.9977
	100.0000

"the Nizoral® Product"

Component	Weight %
ketoconazole	2.0
propylene glycol	
stearyl alcohol	
cetyl alcohol	
sorbitan stearate	
polysorbate	
isopropyl myristate	
sodium sulfite	
water	

A. Antiinflammatory Study

A phase III clinical trial in the United States was conducted to assess the relative antiinflammatory properties of the Combination Product, the Ketoconazole Product, the Desonide Product and the Placebo Gel Vehicle.

In this double-blind, randomized, vehicle-controlled parallel clinical study, a total of 450 patients was tested. The patients were men and nonpregnant, non-lactating women, at least 18 years of age, with clinical signs and symptoms of seborrheic dermatitis. All patients exhibited a rating score of 2 (moderate) or 3 (severe) for erythema and scaling and at least a rating score of ≥ 1 (mild) for pruritus. In addition, a baseline global evaluation score of at least 3 (moderate) for disease severity as determined by an investigator was required for study entry. The breakdown of the patient scoring is indicated below:

Parameter	Mild	Moderate	Severe
Global Evaluation	0	80%	20%
Erythema	0	85%	15%
Scaling	0	84%	15%
Pruritus	39%	51%	10%

One hundred and fifty (150) patients received the Combination Product, 150 patients received the Ketoconazole Product, 75 patients received the Desonide Product and 75 patients received the Placebo Gel Vehicle. All patients were randomized such that the studied medication was applied to the affected area(s) once daily for 14 days and followed through Day 28. Affected areas included the scalp hairline, the post-auricular area, the eyebrows, the bridge of nose, the naso-labial folds and the sternum. At each visit (days 0 (baseline), 3, 7, 14 and 28), the investigator evaluated signs and symptoms of erythema, scaling and pruritus. Each was rated on an interval scale of 0 (none) to 3 (severe), taking into account all areas of involvement. An investigator's global evaluation was conducted on days 0 (baseline), 7, 14 and 28.

The primary parameter of efficacy was the proportion of patients that were effectively treated at Day 28 of the study. Effectively treated refers to those patients who had the following assessment scores:

(i) an erythema and scaling score of 0 (none); or 1 (mild) if the baseline score was 3 and

(ii) a global status score of 0 (clear) or 1 (almost clear) if the baseline score was 3 or greater.

The Cochran-Mantel-Haenszel (CMH) row-mean scores test statistic was used to compare the treatment results between the Combination Product and the Ketoconazole Product, the Combination Product and the Desonide Product and the Combination Product and the Placebo Gel Vehicle. The CMH general associate test statistic was used to compare treatment contrasts on day 28. CMH tests were stratified by grouped study center and the Breslow-Day test was used to test for homogeneity of the odds ratio across grouped study centers.

Pre-study expectations, which were the rationale for the development of the Combination Product, were that the Combination Product would provide superior results due to the dual mechanism of action of the ketoconazole and desonide components contained in the Combination Product compared to the Ketoconazole Product (which lacked the desonide component) and the Desonide Product (which lacked the ketoconazole component). More specifically, it was rationalized that the ketoconazole would target the fungal aspect of seborrheic dermatitis while the desonide would provide relief for the inflammatory aspect (*e.g.*, erythema, scaling and pruritus) of seborrheic dermatitis. Unexpectedly, however, a post-hoc analysis of the results of the study indicated that the Ketoconazole Product was more effective than the Combination Product in alleviating not only the overall seborrheic dermatitis disease state (as shown by the attached global score graph representing day 28) but also the inflammatory factors associated with the seborrheic dermatitis (as shown by the attached combination score graph representing day 28). Both the Desonide Product and the Placebo Gel Vehicle were observed to be less effective than either the Combination Product or the Ketoconazole Product on the primary assessment time point (day 28).

There is no teaching in the cited references of these observed results – *i.e.*, that an anhydrous gel composition lacking a steroidal component is superior in alleviating inflammation compared to the corresponding composition containing a steroidal component. Further, there would be no reasonable expectation of success by a skilled artisan to formulate and use an anhydrous gel composition without a steroidal component in the treatment of a topical inflammatory disease. As stated above, the development rationale for the Combination Product was an expected superiority of the Combination Product over the Ketoconazole Product.

B. Cumulative Irritation Study

The purpose of this double-blind study was to determine the relative cumulative irritation potential of the Combination Product, the Ketoconazole Product, the Desonide Product and the Placebo Gel Vehicle using a standard and accepted testing methodology.

A total of 29 subjects was tested. The subjects were healthy men and nonpregnant, non-lactating women, at least 18 years of age, whose skin pigmentation did not interfere with the reading of the skin reactions. Absorbent patches separately containing each of the four products applied to 3 cm^2 area in an amount of 0.12 to 0.13 grams were placed on a subject's back at a designated site. Patches were prepared no more than 2 hours prior to application of the patches to the backs of the subjects. The patches remained in place for 24 hours, except on Saturdays when they remained in place for 48 hours. After 24 (or 48) hours, the patches were removed. At least 5 minutes after patch removal, the site was evaluated using a 5-point scale grading system. The sequence of applying medications, patching and reading was repeated daily (except Sundays), with application of the same four products being studied to the same sites for 21 consecutive days. Each subject was scheduled for a total of 19 visits, which resulted in 551 scheduled visits for the evaluable subject population. Only 4 of the 551 planned visits were missed, thus allowing for 547 evaluations of the four products being studied.

The grading system was as follows: "Grade 0" (no sign of irritation); "Grade 1" (slight erythema); "Grade 2" (noticeable erythema with slight infiltration); "Grade 3" (erythema with marked edema); and "Grade 4" (erythema with edema and blistering). A technician experienced and trained in reading patch test skin reactions made all evaluations. If a severe skin irritation (Grade 4) was observed at any site, no further applications were made to that site and the maximum score (Grade 4) was assigned to that site for the duration of the study. Other signs of skin reactions to the four products being studied, such as dryness, cracking, peeling, *etc.*, were noted as comments. Evaluations for all subjects were recorded by the product being studied on daily grade sheets for each grade day.

The total score for each product being studied was calculated by totaling the score for each score grade. This was accomplished by multiplying the grade by the number of times it was reported. For example, four Grade 4 scores resulted in a total score of 16. Based on this methodology, the Combination Product was the least irritating with a total score of 100, followed by the Ketoconazole Product with a total score of 119, the Desonide Product with a total score of 138, the Placebo Gel Vehicle with a total score of 219 and the Nizoral® Product of 657. These results are depicted in the attached bar graph entitled "Cumulative Irritation Comparison."

These results were unexpected for at least two reasons. First, pre-study expectations were that the Nizoral® Product would be less irritating to skin than the Ketoconazole Product because the Nizoral® Product formulation is aqueous-based while the Ketoconazole Product is alcohol-based (*i.e.*, anhydrous) and contained no steroidal component. Conventional knowledge in this art teaches that alcohol-based topical formulations are significantly more irritating to skin than water-based topical formulations.

Surprisingly, however, an analysis of the results of the study indicated that the Nizoral® Product had a cumulative irritation index of 5.5 times greater than that of the Ketoconazole Product.

A second unexpected result was the minimal observed difference between the cumulative irritation index of the Combination Product, which contains a steroidal component, and that of the Ketoconazole Product, which does not contain a steroidal component. Conventional knowledge in this art teaches that the presence of a steroid in a topical formulation serves to minimize skin irritation caused by other components of the formulation. The fact that the Ketoconazole Product differs only slightly from the Combination Product in its degree of irritation to skin is therefore surprising and very desirable, given the negative health impact associated with the use of steroids.

C. Antifungal Activity Study

The purpose of this study was to compare the relative clinical response of patients suffering from seborrheic dermatitis to the Ketoconazole Product and the Nizoral® Product. The two products being compared were not tested in the same study. Rather, there was one study comparing the Nizoral® Product with the corresponding placebo cream vehicle that was reported in the Journal of the American Academy of Dermatology 12(5), 852-856 (1985). A second study, which involved a recent comparison of the Ketoconazole Product with the corresponding placebo gel vehicle, adhered to the same protocol described for the testing of the Nizoral® Product conducted in 1985, except that the Ketoconazole Product was administered once a day while the Nizoral® Product was administered twice a day. Because the protocols for the historic first study and the second study were otherwise identical, a direct comparison between the Ketoconazole Product and the Nizoral® Product is possible. The protocol is summarized below.

A total of 37 patients suffering from seborrheic dermatitis were examined at eight sites and graded numerically at each site based on four categories on a 0 to 3 grading scale. A score of "0" indicated clear skin, "1" indicated a mild disease state, 2" indicated a moderate disease state and "3" indicated a severe disease state. The eight examined sites were scalp, hairline, eyebrows, bridge of nose, nasolabial folds, ear canal, posterior aspect of ear and chest. The four categories evaluated were erythema, scaling, papules and pruritus. The maximum score obtainable at each visit was 96 (*i.e.*, a score of 3 multiplied by 4 different categories at 8 sites).

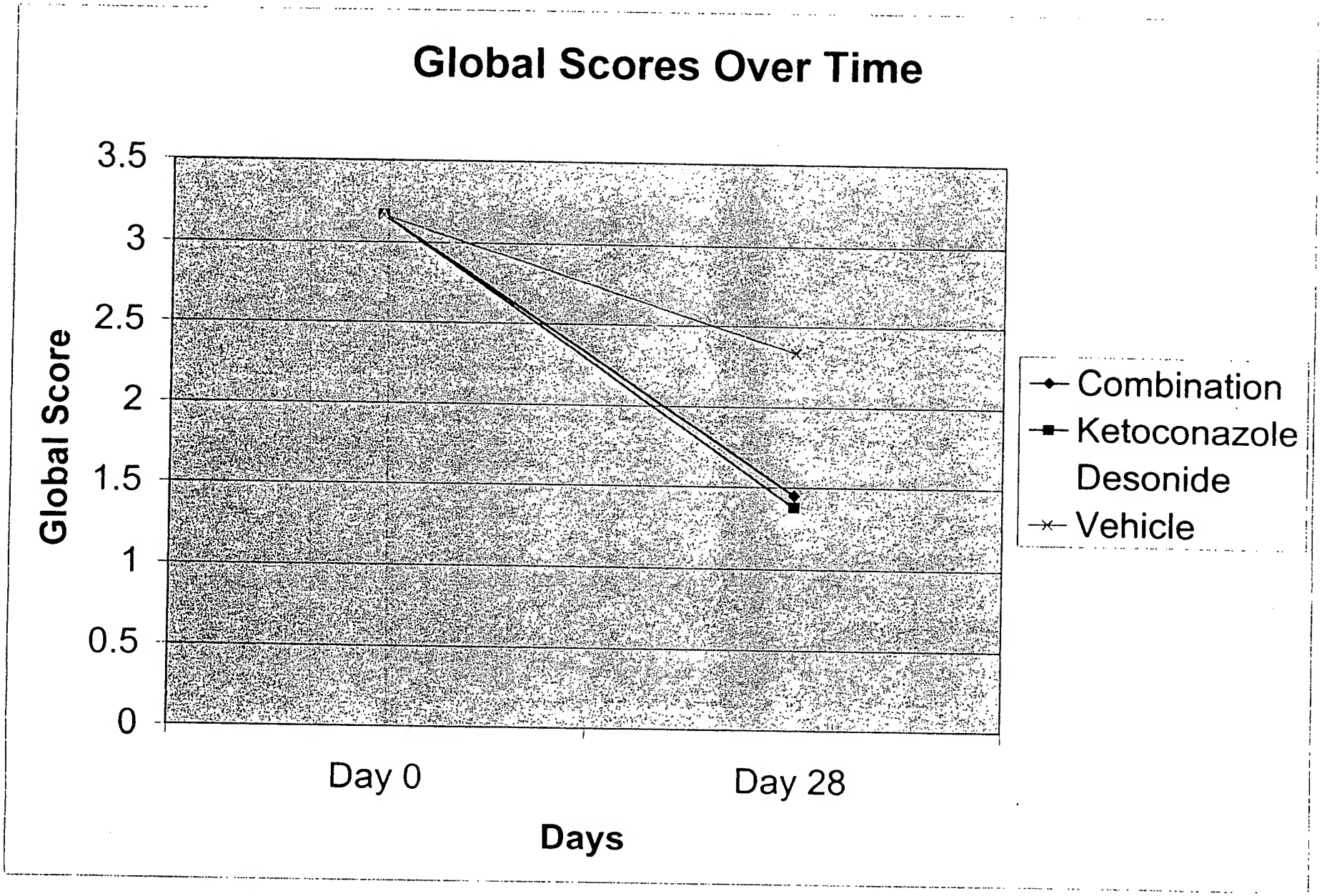
Swabs were obtained for visual assessment of *Malassezia ovalis* (*Pityrosporum ovale*) from the frontal scalp, occipital scalp, right ear and face (eyebrows, bridge of nose and nasolabial folds). The patients were assigned either the Nizoral® Product or the Ketoconazole Product in a randomized fashion and were instructed to apply the assigned product to the scalp, face and ears, twice a day for the Nizoral® Product and once a day for the Ketoconazole Product. No other topical or oral medications considered as

therapy for seborrheic dermatitis were allowed for the duration of the study. The patients were evaluated at two weeks. On each visit, the eight sites were graded numerically for the four categories. The patients received a global evaluation at the end of the study. The global evaluations ranged from total clearing (95-100% improvement), good (75-95% improvement), fair (50%-75% improvement) and poor (less than 50% improvement). Unexpectedly, the Ketoconazole Product had a global score after two weeks of 68.90% under a once-a-day regimen of administration compared to a global score of 49.50% for the Nizoral® Product under a twice-a-day regimen of administration. These results are depicted in the attached bar graph entitled "Reduction in Symptom Severity of Seborrheic Dermatitis." Such a result suggests that the anhydrous gel formulation of the Ketoconazole Product provides enhanced penetration of the ketoconazole through the epidermis compared to the aqueous cream formulation of the Nizoral® Product. The effect of this enhanced penetration is sufficiently significant such that once-daily dosing of the Ketoconazole Product over a two-week period results in a more effective treatment of seborrheic dermatitis than twice-daily dosing of the Nizoral® Product over the same time period.

4. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

October 13, 2006
Date

Geert Cauwenbergh, Ph.D.


Global Scores Over Time
Global Score
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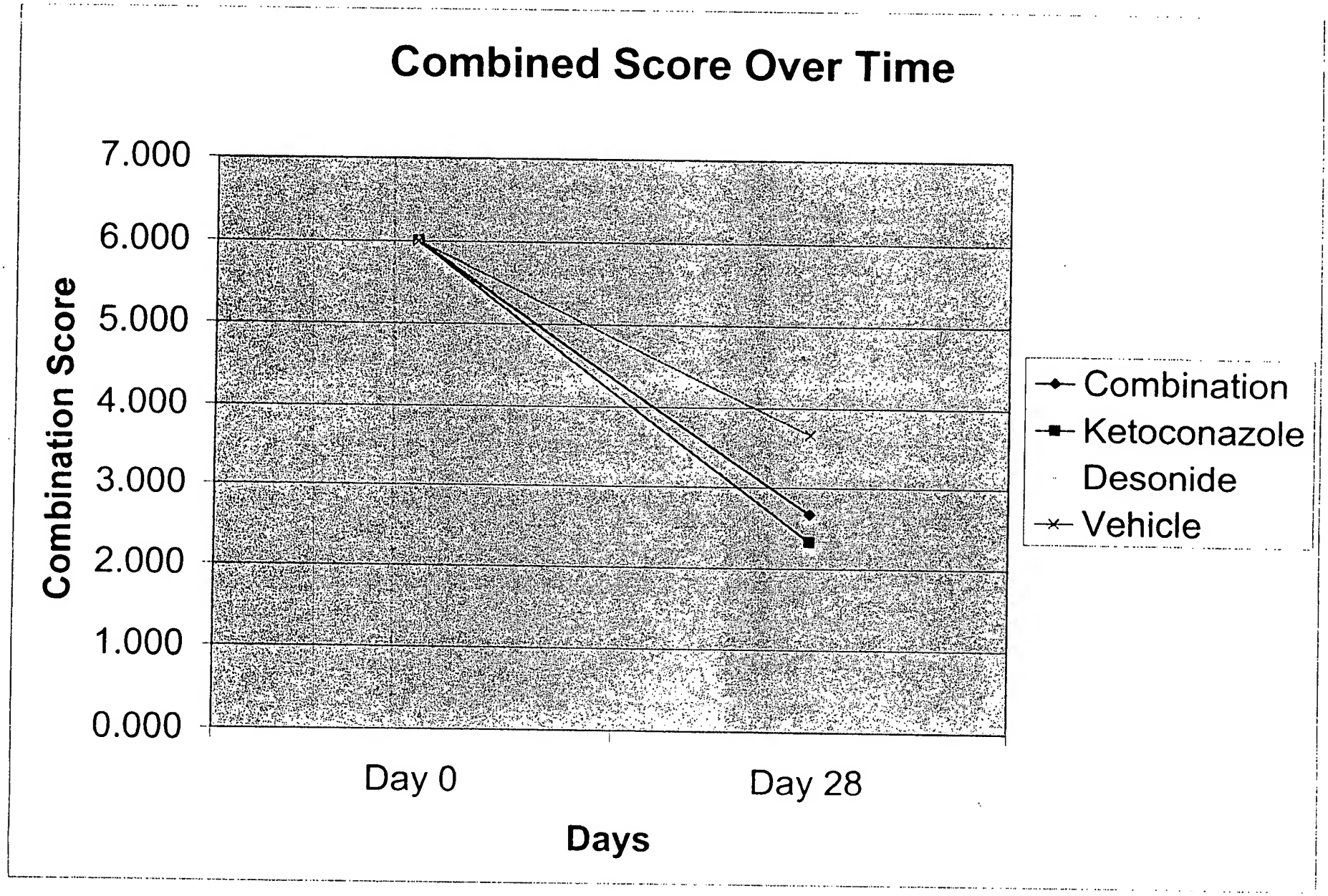
3
2.5
2
1.5
1
0.5
0
Day 0
Day 28
Days
Combination
Ketoconazole
Desonide
Vehicle


Combined Score Over Time
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6.000
5.000
4.000
3.000
2.000
1.000
0.000
Combination Score
Day 0
Day 28
Days
Combination
Ketoconazole
Desonide
Vehicle

Cumulative Irritation Comparison
Total Irritation Score
After 3 weeks
700
600
500
400
300
200
100
0
Combination Product
Ketoconazole Product
Nizoral Product
Desonide Product
Gel Vehicle
Product

Reduction in Symptom Severity of Seborrheic Dermatitis